

Editorial Focus

Burn injuries – is antithrombin back on stage in critical care?

Wolfgang Korte^{1,2}, Lukas Graf¹

¹IKCH, Kantonsspital St. Gallen, St. Gallen, Switzerland; ²University of Bern, Bern, Switzerland

Lavrentieva et al. (1) report in this issue of *Thrombosis and Haemostasis* a randomized study on the early use of antithrombin (AT) concentrate in severely burned patients. This paper seems important for various reasons. Burn injuries are not infrequent; it is estimated that in the United States alone, approximately 2.5 million burn injuries occur every year. Among these, 75,000 patients are hospitalized and of those hospitalized, 20,000 have major burns involving at least 25% of their total body surface. Despite the fact that survival from burn injury has increased, mortality is still high. A coagulopathy has been repeatedly identified as a risk factor for increased morbidity and mortality in the early post burn period as well as in later clinical course.

Although the exact pathophysiology behind this coagulopathy has not been completely elucidated yet, the body of knowledge in this area has markedly increased over the past years.

It has been shown early on that the coagulopathy observed in burn patients shows a high fibrin(ogen) turnover, indicating the presence of a hypercoagulable state (2, 3). It is therefore not surprising that levels of anticoagulant proteins are decreased in burn patients, likely due to consumption (and loss) early in the post burn period (3, 4). Other possible explanations such as dilution due to fluid treatment (4) have to be considered as well. Besides anticoagulant activity, AT mediates proteinase inhibition (which is thus reduced in deficiency states), leading to increased proteinase activity. An increase in proteinase activity has been incriminated as a risk factor for adverse outcome in burn patients (5, 6). This idea is also supported by the fact that proteinase inhibition improves survival in animal models (7). Thus, decreased AT activity in the early post-burn period seems to be induced through multiple mechanisms and to have multiple adverse effects. Research into the potential benefit of AT replacement therapy in this setting is therefore certainly warranted.

Animal studies suggested that AT replacement not only has anticoagulant but also an immunomodulatory effect, attenuating T-cell response and thus inflammatory pathways (8); such results easily allowed to postulate that AT replacement therapy could indeed be of benefit to burn patients. Although an early study found no benefit of using AT replacement therapy (9), a further

controlled clinical trial did suggest a benefit but failed to show significant differences, likely due to the small sample size (10). Interestingly, the same group reported a significant (beneficial) impact of AT replacement on pulmonary parameters in burn patients (11). This observation was reproduced in an animal model of AT replacement therapy (12), while the use of heparin could not achieve this effect (13). Other observational studies repeatedly suggested a clinical benefit of higher versus lower AT levels in the early post-burn period (14–16).

It is the merit of the work by Lavrentieva et al. (1) to show in a prospective randomized trial that AT replacement therapy early in the post-burn period might protect from increased morbidity and mortality. As the association of overt disseminated intravascular coagulation and morbidity and mortality in critically ill patients is a well known phenomenon, it is not surprising that this association can also be documented in burn patients, as indicated by the results of this study. This also hints to the relative strength of this study: the patient population enrolled was apparently not highly selected, i.e. it seems that a "real world population" was treated. The results are therefore very impressive: to see a significant 25% reduction in overall mortality by day 28 after a relatively simple, usually well tolerated intervention seems to take treatment en route towards the "magic bullet".

But if something looks like a "magic bullet", always think twice. The strength of the study also harbours a potential weakness: the fact that essentially unselected patients were treated suggests that the patient population of this study might have been somewhat heterogeneous. In heterogeneous populations, sufficiently large sample sizes are necessary to allow the conclusion that the results can also be applied to other (heterogeneous) patient populations. A sample size of 31 patients is likely not sufficient to allow this conclusion. The study, however, has done a great deal to provide hypothesis generating data needed for future trials.

AT replacement therapy is still burdened with the failure of an earlier, well-sized randomized trial in sepsis (17); but detailed analysis shows it was likely co-medication and not the use of AT itself that made the trial fail (18). Therefore, adequately powered confirmative studies are needed before AT replacement can be

Correspondence to:
PD Dr. Wolfgang Korte
IKCH, Kantonsspital
CH-9007 St. Gallen, Switzerland
Tel.: + 41 71 494 39 73, Fax: + 41 71 494 39 73
E-mail: wolfgang.korte@ikch.ch

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adopted as an evidence-based therapy in the early postburn period. The stage for cautiously and meticulously developed, adequately sized and industry sponsored intervention trials is set.

Time might have come to get things moving again towards AT replacement therapy in critical care.

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